FOOD AND DRUG ADMINISTRATION

CENTER FOR TOBACCO PRODUCTS

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

(TPSAC)

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White Oak Conference Center

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Silver Spring, Maryland

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I N D E X

P R O C E E D I N G S

Call to Order

DR. SAMET: Good morning. We'll go ahead and get started with the continuation of the TPSAC meeting. Just so everybody is aware, due to the weather exigency, we will be ending early today. And I think it's likely, just checking around the table when various committee members are intending to leave, we probably should be done hopefully by midday. So we will aim for that. So we're going to need to work hard and intensively this morning.

So we began, if you remember, yesterday, with some of today's agenda, discussing chapters 1 and 2. We have 3, 4, 5, 6, and 7 left; the latter two really not particularly underway yet, but we can talk about the general approach that will be taken.

Then what you have in front of you is just sort of broad discussion questions that are some of the major topics that we need to cover when we begin the talk in general. So I think what I'll do is I'll turn to you – sorry. Caryn has to read her

statement, then I'll turn to you for chapter 3.

Conflict of Interest Statement

MS. COHEN: Okay. Thanks. The Food and Drug Administration, FDA, is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representatives, all members and non-voting members are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict-of-interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict-of-interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members of this committee are in compliance with federal ethics and

conflict-of-interest laws under 18 U.S.C. Section 208. Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflict of interest when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary, to afford the committee essential expertise. Related to the discussions of today's meeting, members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing,

patents and royalties, and primary employment.

Today's agenda involves receiving an update on the Menthol Report Subcommittee and receiving and discussing presentations regarding the data requested by the committee at the March 30-31, 2010 meeting of the Tobacco Products Scientific Advisory Committee.

This is a particular matters meeting, during which general issues will be discussed. Based on the agenda for today's meeting, and all financial interests reported by the committee members, no conflict-of-interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all committee members to disclose any public statements that they may have made concerning the issues before the committee.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Daniel Heck and John Lauterbach, and Mr. Arnold Hamm are participating in this meeting as non-voting industry representatives, acting on behalf of the interests of the tobacco

manufacturing industry, the small business tobacco manufacturing industry, and tobacco growers, respectively.

The role at this meeting is to represent these industries in general and not any particular company. Dr. Heck is employed by Lorillard Tobacco Company; Dr. Lauterbach is employed by Lauterbach and Associates, LLC; and Mr. Hamm is retired. FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

I would also like to remind everyone present to please silence your cell phones if you have not already done so. And I would also like to identify the FDA press contacts, Jeffrey Ventura and Tesfa Alexander. And if either or both of you are here, please stand up. Thank you.

Introduction of Committee Members

DR. SAMET: Okay. And I guess just for the sake of form, we should do committee introductions. Dan?

DR. HECK: Dan Heck with the Lorillard

Tobacco Company, representing the tobacco manufacturers.

DR. LAUTERBACH: John Lauterbach, Lauterbach and Associates, representing small business tobacco manufacturers.

MR. HAMM: Arnold Hamm, representing United States tobacco growers.

DR. KAROL: Susan Karol, the Indian Health Service chief medical officer.

DR. BACKINGER: Good morning. Cathy Backinger with the National Cancer Institute, representing the National Institutes of Health.

DR. WAKEFIELD: Good morning. Melanie Wakefield from the Cancer Council Victoria in Melbourne, Australia. And I'm on the committee representing the views of marketing and communication.

DR. BENOWITZ: Neal Benowitz, the University of California San Francisco, internal medicine, pharmacology, cardiology.

DR. DELEEUW: Karen DeLeeuw, Colorado Department of Public Health, representing

government.

DR. HATSUKAMI: Dorothy Hatsukami, University of Minnesota, professor of psychiatry.

DR. HENNINGFIELD: Good morning. I'm Jack Henningfield. I provide risk management health policy services at Pinney Associates, and I'm adjunct professor at the Johns Hopkins University School of Medicine.

DR. CLANTON: Mark Clanton, chief medical officer of the High Plains Division of the American Cancer Society, pediatrics, public health, and oncology.

DR. HUSTEN: Corinne Husten, senior medical advisor, Center for Tobacco Products, FDA.

DR. ASHLEY: David Ashley. I am director of the Office of Science at the Center for Tobacco Products at FDA.

DR. SAMET: Okay. Good. Thank you. Then, Neal, why don't we move to chapter 3?

DR. BENOWITZ: Can I do it from here?

DR. SAMET: Wherever you want.

Chapter 3 – Physiological Effects

Neal Benowitz

DR. BENOWITZ: I'd rather just do it from here.

Chapter 3 will be addressing the pharmacologic issues for menthol that might relate to smoking behavior and resulting health risks.

I think this chapter serves as a background chapter to understand why there might be concern about menthol, what menthol could possibly do that could affect smoking behavior.

So the first section looks at the chemistry of menthol and menthol isomers, examines the botanical source of menthol, as well as synthetic menthol, the structures, the questions of stereoisomers that are present in tobacco, the process by which menthol is added to tobacco, concentrations of menthol in cigarette tobacco, examining both the very low levels that are present in many cigarettes, and then the various levels in menthol-characterized cigarettes, including relationships to tar/nicotine yields, and then, the transfer efficiency of menthol and effects of

cigarette ventilation on the transfer of menthol.

The next section examines mechanisms of action and summarizes the pharmacology of menthols acting on the TRPM8 receptor, which results in the cooling effects, and then the TRPA1 receptor, which results in irritant effects, how on afferent nerves, and a little bit about the afferent nerve pharmacology, the primary effects of cooling and irritation, topical analgesia, which is certainly seen in skin, the question of menthol-enhancing, penetration of drugs and chemicals across the skin, the issue of receptor desensitization of nociceptic, or ceptive, or pain responses.

There's literature looking at interactions of menthol nicotine, the question of whether menthol desensitizes to the irritant or painful effects of nicotine. It might allow a person to take in higher levels of nicotine without an adverse response, and we'll look at that literature.

The next section will look at kinetics and metabolism. We'll discuss the bioavailability of

menthol from cigarettes, which is basically how much menthol in a cigarette gets into the smoker, the metabolism of menthol, its various pathways, the half-life of menthol, effects of menthol on drug metabolism, especially nicotine metabolism, and then the data examining the proposition that menthol might inhibit glucuronidation and detoxification of the nitrosamine, NNAL.

Then the next section will examine clinical effects, so, again, it'll look at the cooling, soothing, and irritant effects of menthol in relation to concentrations in various cigarettes, respiratory effects, including the perception of increased nasal patency, the effects on breath-hold time, and cough suppression, and then some of the cardiovascular effects that have been observed, mostly with oral menthol, and effects on the intestinal smooth muscle.

Then the final part will be to just go and say that these are the ways that menthol could potentially affect smoking behavior. So menthol cooling effects are consistent with facilitation of

youth experimentation and transition to addiction. Menthol sensory effects are consistent with enhance reinforcement and enhanced dependence, and that the menthol cooling and soothing effects and/or desensitization of nicotine effects are consistent with greater inhalation of smoke per cigarette, especially in light smokers.

So, again, this chapter sets up the potential concerns raised by the pharmacology of nicotine, which then later data we'll examine and look at the evidence for.

So that's a quick overview of what this chapter will present.

DR. SAMET: Okay. Thank you. I think what we should do is just open this up for discussion. I have one question. When you're talking about mechanisms of action, you talk about enhanced penetration of drugs and chemicals across skin. But what about epithelial surfaces, in general, the respiratory epithelial in the upper airway?

DR. BENOWITZ: Well, I think that's the obvious concern for smoking, and there has been a

lot of interest about that. I'm not seeing a lot of data on enhanced absorption from the airway for menthol, but certainly, the potential is there, based on what we know about skin.

DR. SAMET: Other questions or comments about this material? Yes, Jack?

DR. HENNINGFIELD: Something that came up yesterday that we had some discussion about was other substances related to menthol or that may be menthol substitutes. And I think, in all of the chapters, we need to find the balance of focusing on the topic that we've laid out but being open to include things that come along the way.

So my guess is that with respect to other substances, there may not be a lot of information that we'll come upon, but if there is other information on substitutes and analogs, I hope we can include that, at least get it on the radar screen.

DR. BENOWITZ: Yes. I think that will be included in a section on menthol chemistry.

DR. SAMET: So just to make a comment way

over my head, the activation of the TRPA1 receptors -- I mean, there are certainly other things in tobacco smoke that do that, formaldehyde, presumably some of the other irritants. So how beaten up are those receptors by tobacco smoke, and what happens with yet another agent in tobacco smoke that activates that receptor?

DR. BENOWITZ: It's hard to respond to how beaten up are they.

DR. SAMET: That's the technical term.

DR. BENOWITZ: There are certainly multiple irritants. And the big issue, really, is not so much the irritation effects; it's the desensitization of irritation effects. And so when you stimulate these receptors, you then desensitize them. And then the idea would be that you allow exposure to irritants that you might not ordinarily allow exposure to. So I think that's a big concern about the irritants.

Also, menthol can substitute. If there's less tobacco smoke, less nicotine, there's less intrinsic irritation, but there's more menthol,

then menthol can give some of the impact, the smoke that might otherwise have been carried by the rest of the smoke. And so it does interact. I'm not sure that there have been studies where you simultaneously apply menthol and other constituents, but clearly there's interaction.

DR. SAMET: Dan?

DR. HECK: Yes. I think the committee, and certainly the industry report, will try to discuss this area as well. But the committee should be alert, I think, from this literature, for the importance of the dose response and level of menthol relative to the predominance of cooling effects versus irritative effects.

I know in some experimental systems, at experimental research levels, we see some of these effects. And I think the important thing will be for us to try to extrapolate this to the realistic levels of exposure that may accompany smoking. So that's just a comment.

DR. SAMET: I had one more comment, too, Neal. I think, in fact, your comment leads into it

because our charge is to discuss menthol in cigarettes, which means that we have a substantial proportion of cigarettes with lower concentrations of menthol than those that have menthol as a characterizing additive.

So that does raise a question in thinking about your bottom line slides, that making some inferences about dose response for some of the key consequences may be important to addressing menthol cigarettes and menthol in cigarettes.

DR. BENOWITZ: Yes.

DR. SAMET: Yes, John?

DR. LAUTERBACH: Dr. Samet, to that point, I'm concerned about the positioning of these experiments, detailing when menthol's been applied to membranes, and then enhancing transporter materials through those. There are many compounds in tobacco, some of which are there more than in menthol and mentholated cigarettes, which are going to basically have the same effect. So if you just took the common, safe, normal cigarette smoke, a non-menthol one, or even from just a single grade

of tobacco and applied that on those membranes, you'd likely see the same effect.

DR. BENOWITZ: That's certainly worth mentioning. If you have some literature about that, I would like to see that. That'd be great. Thanks.

DR. SAMET: I do remember, Neal – and perhaps somebody else remembers this better than I -- the literature on probably 20 plus years ago, on lung epithelial permeability, remember, that was done with some sort of radioactive tracer. And I don't know whether any of those experiments were done with menthol versus non-menthol cigarettes. Remember, it was a very crude, sort of whole lung permeability.

DR. BENOWITZ: Well, no. There is a lot of evidence about smoking, in general, enhancing permeability of drugs, bronchodilators, a bunch of things. So there's good literature about that. I don't know any studies that have tried to separate out --

DR. SAMET: Right.

DR. BENOWITZ: -- menthol versus other aspects of smoke.

DR. SAMET: Okay. Other comments about chapter 3? Yes, Mark?

DR. CLANTON: I think Mr. Lauterbach's comment reminded me that we're really dealing with a very complex system and matrix of chemicals when it comes to the impact of cigarette smoke, in general, on the respiratory system. But I did want to ask, given, I guess -- is it D menthol being more irritating than L, or are they equivalent? I remember you made a mention of that yesterday.

DR. HECK: I'm sorry. I don't know with regard to irritation, but certainly with regard to the cooling effect, it's L menthol that is what's prominent.

DR. CLANTON: So to the degree that L and D menthol have some irritating effects, is there any data looking at sputum production as it relates to cigarettes that are characterized by menthol versus those that have lower levels of menthol?

DR. BENOWITZ: I have no seen any literature

on those types of clinical effects.

DR. CLANTON: Okay.

DR. BENOWITZ: If anyone else has seen them, I would love to get a copy of those papers. But I've never seen any work trying to separate out menthol versus non-menthol, in terms of pulmonary pathology.

DR. SAMET: Yes, David?

DR. ASHLEY: Neal, I notice in here that you said you've got a section on botanical sources of menthol for cigarettes and tobacco. Are you going to mention in there also that there are certain synthesized versions of menthol in certain products?

DR. BENOWITZ: Yes, I will.

DR. SAMET: Neal, just one other question in terms of sort of general approach, there's a peer-reviewed literature. How much do you see yourself drawing on documents, presentations, industry documents, and so on here? Will this largely be based on what's in the peer-reviewed literature?

DR. BENOWITZ: The pharmacology will. Some

of the issues, such as how menthol is added to cigarettes, I basically used industry presentations for that. I think that the pharmacology's pretty much peer reviewed.

There are some industry research studies that are cited in some of the review papers, which I don't think are published. I may need to just mention those and their source, but I will not be able to look at the primary data for those papers. But I think most of this section, the work is published.

DR. SAMET: Okay. Good. Anything else?

[No response.]

DR. SAMET: Okay. Then let's move onto chapter 4. I was going to say, Karen, you're going to do that.

DR. DELEEUW: I just want to make sure Dr. Henderson isn't on the phone.

DR. SAMET: Do we know?

MR. GRAHAM: She's on the phone and waiting to do the presentation.

Chapter 4 – Patterns of Smoking

DR. DELEEUW: Okay. Thank you.

All right. This is patterns of menthol cigarette smoking in the U.S. Basically, we're going to be describing the pattern of menthol cigarette use in the U.S. populations and describing prevalence by race, ethnicity, gender, and other social factors. And two potential other things we're going to be looking at is menthol use among persons with mental illness and substance abusers. So we're looking and seeing what we can find about that.

A brief discussion of methods, basically, we're relying on three publications that had basically done the synthesis of the data, and then also the presentation by Dr. Caraballo, which included a detailed analysis of the original data, a brief discussion of the methods, and the data that we're using.

This is just a look, a little bit more in-depth look at the four studies we're relying on, study periods, population, limitations, and their

definitions of menthol cigarettes that were used in those studies.

This is a slide we took from an industry presentation, which is basically just to show the increase in menthol cigarette use, especially since the mid '50s and the decrease in non-menthol cigarette use.

Here, we're just looking at menthol cigarette use, past month, 18 and over, and 12 through 17, obviously by racial ethnic groups. It's a little difficult to see the percentages on the slides because they're dark. And I'm not going to spend a lot of time on the actual data, but just to give everyone an idea of what we're including.

Percent of non-menthol cigarette use, so the flip of the previous slide. This is percent to menthol cigarette use among past month, cigarette smokers age 12 and older by gender, and, obviously, as we all know, higher use among females.

This is percent menthol cigarette use, past month, age 12 and older, by race, ethnicity. And the asterisks obviously indicate statistically

significant differences.

This slide basically just articulates menthol use in terms of numbers, so 1.1 million adolescents, 18.1 adults, 18 years and older, for a total of about 19.2 million menthol smokers annually.

This is the prevalence of menthol cigarettes by sociodemographic categories. So you can obviously see on the slide, blacks have the highest prevalence and on down. I think, of interest, is really looking at, more in depth, what we would consider more vulnerable populations, including unemployed family income of less than $10,000 and low education levels, and a continuation of that slide.

This is a slide showing the prevalence of mentholated smoking for men by the sociodemographic categories. So, obviously, African-Americans, annual family income of less than 10,000, and smoking 6 to 10 cigarettes per day are probably of significance.

This is the same data looked at for women.

Again, African-Americans, low family incomes, and low levels of education, and then, again, a higher prevalence among 18- to 24-year-olds and 45- to 64-year-olds.

This is basically national rates of mentholated cigarettes, smoking by race, ethnicity. So across all races and ethnicities, women smoke more than men, and 18- to 24-year-olds had the highest prevalence. And here we have some adjusted odds ratios.

This just looks at trends, age 12 to 17 from 2004 to 2008. This is adult smokers, so 18 to 25 and over 26. This is 12 years and older by gender. And, again, we continue to see females smoking more menthol cigarettes. This is by ethnicity, 18 years and older by gender; so this is the men.

This is, again, by race, ethnicity, 18 years and older, by gender. So this is a slide describing women menthol smokers; by family income, 18 and older, and a brief discussion of the limitations. And I think that's it.

DR. SAMET: Okay. Thanks. And I have one

thought. And if you go back to the table, where you described the surveys, so here, I have these somewhat different questions. And I wonder if we need a section here on reporting of smoking, reporting of brand, what we may know, if anything. And I don't know if there's literature on comparison of approaches to assessing menthol use.

In other words, we've heard discussion about different findings, and different surveys, different methodologies. And maybe you're going to need an introductory section that, perhaps, talks about issues that may affect these reports. I mean, this is sort of central, and we know that self-reported data may suffer from various forms of misclassification, ranging from understanding what brand people are smoking, understanding whether they are not smoking menthol cigarettes, the use of usual versus what's happened in the last 30 days, and so on. And these subtleties often lead to differences in survey performance.

So maybe we need some general introductory comments here. I don't know -- I probably

should -- how well the literature might be developed on this particular aspect of reported smoking that is menthol use. But I think that would be useful, anticipatory material to discussion, where you point to recall as one of the limiting issues.

DR. DELEEUW: Thank you.

DR. SAMET: Cathy?

DR. BACKINGER: I think that that has been published, and I want to say maybe Gary Giovino's done it, just kind of the strengths and weaknesses of the different national surveys. I'm not quite sure; maybe not on menthol, but just looking at the national surveys themselves, the methodology, and the strengths, and weaknesses. But I guess the other thing I wanted to point out is that, even with the strengths and weaknesses of the various national cross-sectional surveys, I mean, the government relies on those surveys to track progress for healthy people goals.

So I think, even with some limitations, those are the data that we have. And barring other

data, that's what we rely on, and we've relied on that for years to track our healthy people objectives. So I think that should be a statement that's included in the report, in that section.

DR. SAMET: Other questions or comments? You're a quiet group this morning.

DR. DELEEUW: Patricia, did you have anything you wanted to add?

DR. HENDERSON: Good morning, everyone. Yes. With the presentation that was given by NCI yesterday on the new analysis, is that something that we should also include or how should we do that?

DR. SAMET: Karen, do you want to comment?

DR. DELEEUW: Yes. I guess I would assume that we would look at that data and see.

DR. SAMET: Yes. I think there was certainly interest in the data, Patricia. I mean, it's new data, and, certainly, an important new question being asked. And I think these are data that would be useful. We would like to get a little more background on the data.

DR. DELEEUW: Correct.

DR. SAMET: But we thought they would be useful.

Mark?

DR. CLANTON: Patricia, this is Mark. I think we're going to end up sorting out where data goes throughout this entire report. Some data may need to be repeated to make points in different chapters, and in other cases, we may want to save it and aggregate it in one particular chapter.

I'm not sure yet where this should go. I think either this will show up twice in two chapters, with yours being one of them, or we may think about is there another one. And, again, I'm trying to think in terms of the public health impact, could these data be used there as well.

So I'm not sure exactly where those data or that presentation goes, but it will probably go somewhere, I think, in the report.

DR. HENDERSON: Okay. And then, another issue that we were talking about is the National Youth Tobacco data that is available for us. And

they've been tracking that for many years, and whether or not we should have that analyzed, to look at the trends among adolescents for menthol use.

DR. SAMET: Cathy?

DR. BACKINGER: I don't have a response to what Patricia's raising. I just wanted to make a comment on Anne Hartman's presentation yesterday with the caveat that she mentioned those were collected just over May 2010, and we don't yet have the confidence intervals.

So I think at least as far as this particular chapter, it's confirming similar menthol rates among different populations, menthol smoking rates among different populations. So just with a caveat, I think, perhaps, in a different section, maybe in Dorothy's, your section, because it talks about cessation, or at least intentions that, as Mark said, it's probably going to show up in more than one area, but with the caveat that these are preliminary data.

DR. SAMET: Let's see. Let me just go back

one second, Jack.

Patricia, when you were talking about additional survey data on youth, did you have a particular survey in mind?

DR. HENDERSON: Yes, the National Youth Tobacco Survey.

DR. SAMET: Okay.

DR. HENDERSON: Yes.

DR. SAMET: Jack?

DR. HENNINGFIELD: Continuing along these lines of thinking about the different surveys, what they tell us, and also Dr. Clanton's comment about the public health impact, I'm not sure if this chapter is the right place, but it strikes me that here, we have a display of what are the existing major surveilling systems that we have to look at. And that's useful in helping characterize menthol use and anticipating unintended consequences. But going forward, I think we all recognize that other kinds of surveillance may be needed. And, in fact, that's a big part of the Tobacco Control Act.

It strikes me that we discussed issues

yesterday, and concerns, such as contraband use, such as, for example, would 72 percent of current menthol smokers turn to contraband. That seems high to me, but do we have any systems in place that would help us detect that in an accurate, timely fashion? And I'm not sure. That's not the only issue. There are many issues.

So as you're going forward, looking at different surveilling systems, one thing to be thinking about is, what issues have come up, issues and concerns and unintended consequences, that are, frankly, not adequately addressed by these instruments?

For example, with prescription drug abuse, to assess diversion, the National Association for Drug Diversion Investigators; that's a nonprofit that gets the law enforcement working with public health. Maybe something like that is needed here, because now we're talking about potential criminal activity and things outside of our normal -- that's just one example, but the point is to be thinking about what kinds of surveillance systems may be

needed going forward.

DR. DELEEUW: That's a good suggestion, and thank you. And I know on the National Youth Tobacco Survey, that they do talk, particularly ask questions, about how you obtain cigarettes. So there may be some additions we could make to responses to that question that might set us in that direction.

DR. HENNINGFIELD: In some cases, it may be minor modifications of existing instruments, but I think we should be open to the possibility of saying, you know, here's an area that just really isn't adequately covered in approach. Again, I'm not sure that where there is potential criminal activity, that any of these systems are really designed for that.

DR. SAMET: Actually, for future impact of it, Jack's point is important. I mean, the other would be -- I don't want to violate the sanctity of existing surveys and questions, but ways to perhaps think about refining the questions that are used for menthol; is there an agenda for research here

and could things be better sorted out. I mean, this is just something to think about either here or perhaps in chapter 7, I think, how could this set of questions be fine tuned.

It's not trivial to develop these kinds of instruments, and you make changes guardedly. On the other hand, if they're not as sensitive as they should be, for intended purposes or new purposes, then it's always useful to rethink a little bit.

Neal?

DR. BENOWITZ: I'm not sure if this is the right section, but I think it'd be important, at some point in time, to look at menthol prevalence, not just in the last 15 or 20 years, but back through the 1950s, especially if we're looking, say, at lung cancer risk or something like that, where there's a long lag time, and we want to know what the patterns have been over time.

It would also be nice, if there are data available, to be able to estimate how much of brand-shifting there have been. For example, in 1950, 15 percent of people smoked menthol cigarettes, and

now, 30 percent. And, obviously, brands have not been stable over time.

So I think we need some sort of perspective. I'm not sure if it goes in this chapter or in the effects chapter, but I think we should look historically at some of these data.

DR. SAMET: Karen, I had one other question. Maybe this is a comment, something for us to think about. The various tables you've presented with prevalence rates by different characteristics, those are univariate analyses? For some of this, these are just the data stratified by these different characteristics? Is that what we're looking at?

When you look at, for example, the men, you say the prevalence of smoking mentholated cigarettes for men was highest in the following categories. So these are all just sort of stratified analyses, if I understand you correctly?

DR. DELEEUW: I believe so. Is that correct, Dorothy? I mean, Patricia.

DR. HENDERSON: Yes, it is. And then, this

data was actually published in Addiction, and then, at the end, they did a multivariate regression. And we don't have that information on here. But, actually, it is on there, where they did the adjusted odds ratio and saw that for blacks, they're 10 times at a higher risk or a higher rate of menthol use.

DR. SAMET: Okay. Fine. And then, I think as you develop your text, I'll want to have some discussion about how to display the univariate and then what these models mean. So I think we'll have to just take a close look at how things are presented, what they are, and just be very clear about it.

DR. HENDERSON: Right. But I think that's one of the issues that we were having when we were writing this. There's just so much data and a lot of tables; so how do we bring it all together so that it reads well.

DR. SAMET: Right. Yes, Mark?

DR. CLANTON: Just a general comment. I think we need to be very purposeful and clear about

using multivariate versus univariate analyses. They tell us different things. And so, sometimes using multivariate analyses can pretty well eliminate any effect if we're looking at a particular group.

So we need to be very thoughtful, and say if we're using univariate analysis, here's why we're using it, and here's what impact we think these data have. And, in very special cases, talk about multivariate analyses, and also explain why we're presenting that information. Again, it can be misused if those two types of analyses are used inappropriately. So we just need to be very thoughtful about not just presenting it, but drawing conclusions from those two different kinds of analyses.

DR. SAMET: Yes. I think interpretation of these adjusted odds ratios is challenging.

Other comments on this chapter? Dan?

DR. HECK: Yes. Again, just a general comment. I guess we've heard it mentioned a couple times of this new NCI unpublished report, the

intent that we saw yesterday for the first time.

I would encourage the committee to give similar, equitable and full consideration of the rather detailed and learned analysis that Dr. Curtin presented earlier, and again yesterday, on these available datasets, because I think that there was a lot of insightful thought and analysis in those analyses.

DR. SAMET: Thank you. Yes, Corinne?

DR. HUSTEN: I just heard a few comments about maybe some other studies that people feel they might need, or other analyses. And I would just say, if there are studies that you think you need, let us know and we'll try to find them for you, or if there are analyses, we'll see what we can do.

DR. BACKINGER: Just a question, I guess. I don't think Anne is here today. But to follow up with her, I mean, I think yesterday, the discussion was having a little more -- not just for hers; I'm just generally talking about hers specifically. But any of the unpublished data or presentations

yesterday, we talked about kind of requesting a little more background information and methodology.

So will FDA follow up with that? And because the confidence intervals --

DR. HUSTEN: Yes, as long as we know what you're interested in, we can make the contact.

DR. BACKINGER: Because I think that the confidence intervals probably would be ready in time, if not today, now, shortly in time to have that for the report.

DR. SAMET: I think it's probably fair to say we were interested enough in the data presented by Anne, that we would like to have it in, let's say, a more formal presentation, write up a formal report that provides clearer documentation of what was done. I think it was probably straightforward, obviously, but I think we need something like that to go with the slides.

DR. BACKINGER: Sure.

DR. SAMET: Yes, Dorothy?

DR. HATSUKAMI: I just wanted to get a little bit of clarification in terms of what your

selection criteria was for the studies that you chose to use in your chapter. It looks like the one that you describe here, studies that directly compared smoking menthol cigarettes versus non-menthol. But were there other criteria that were used?

DR. HENDERSON: Yes. We decided to focus primarily on the national datasets that are out there and excluded any small studies that were done, as well as any qualitative studies that were out there, because there are a lot of small studies with small sample sizes that we could have used. But we wanted to provide a broad picture of what is happening across the United States and across different populations. We felt like these were probably the best representation of what is out there.

DR. SAMET: I think Dorothy's point is a good one. I think you'll need to say very explicitly how you happened to pick these. I mean, I think they do exactly what you said, but I think you need to be clear.

DR. HENDERSON: Okay.

DR. SAMET: Neal?

DR. BENOWITZ: Yes. There's a quick point about regions; you talk about northeast. I think it might be of interest just to talk a little bit more about what kind of regional variation there is in terms of urban versus rural and things like that, so it's just some background about menthol use throughout the U.S. as opposed to a single figure for the whole country.

DR. SAMET: Melanie?

DR. WAKEFIELD: I guess one issue that may not be captured in population surveys is the prevalence of menthol smoking by some sort of special population groups, so-called vulnerable, subpopulations, some people with mental illness, and so forth. And it may be that there might be no studies relating to that, but that might be a case where you might make an exception to go beyond national data and look for something more localized or specialized.

DR. SAMET: Mark?

DR. CLANTON: Yes. I certainly agree with that, and I think Hawaiian/Pacific Islanders are a great example of a group who would not normally show up in a large, national dataset. However, based on whatever smaller studies we have, it would describe, very nicely, menthol use in those populations. So a very good point. And I want to make sure we at least go after those groups.

I don't know to what degree American Indians, collectively, are represented in these national surveys. But to whatever degree they aren't, there are smaller studies that can be used to describe the incidence and prevalence of menthol in those populations.

DR. SAMET: Okay. Anything else on this chapter, chapter 4? Okay. Thanks. Thanks to Karen and Patricia for getting this started.

Okay. Chapter 5, which I think will take a while.

Chapter 5 – Initiation, Cessation and Marketing

Dorothy Hatsukami

DR. HATSUKAMI: The authors on this chapter

are myself, Melanie Wakefield, Lisa Henricksen, who is from Stanford University, and has some expertise in marketing in youth, and Mark Clanton. And the topics that we're focused on are marketing, initiation, addiction, and cessation.

This is the process by which we are conducting our examination of the information. The sources of documents include peer-reviewed literature, papers written or commissioned by the FDA, including the secondary analysis that was submitted in November 2009, the tobacco industry submissions, and any public comments that we deem to be relevant and databased.

We are preparing tables similar to chapter 4, and these tables will examine each document for the study designed, including subject characteristics, the outcome variables, the results, and strengths and weaknesses of the studies.

So what I'm going to do is I'm going to describe the primary question that we're addressing, and then the questions that we would

like to address within that primary question. So with regards to marketing, the primary question is, does tobacco company marketing of menthol cigarettes increase the prevalence of smoking beyond the anticipated prevalence if such cigarettes were not available, in subgroups within such populations as well?

The primary areas that we're looking at include marketing, branding, and targeting. And then, we will be looking at the relationship between marketing, beliefs, and behavior.

So under the heading of marketing, branding, and targeting, these are the questions that we will be addressing. How are menthol cigarettes marketed? What are the methods used for marketing? How is menthol marketing different from and similar to non-menthol marketing? This is in relationship to price, promotion, product placement, and packaging.

Secondly, we're asking, what does the branding of menthol cigarettes promise about the product and about consumers of the product?

Another question is, what is the content of marketing efforts? What is the evidence to show that marketing provided health-reassurance messages, and are these messages being conveyed either implicitly or explicitly, currently? What other messages are conveyed to potential consumers? That is, are there messages of being refreshing, taste, pleasure, coolness sensation? Who are the target populations for marketing? Is there evidence to show that youth, women, and specific ethnic groups were targeted? How are these target marketing populations selected? And what are the attributes of the different brands of menthol cigarettes that attract people? How do they play a role in attracting target populations?

So the next section is examining relationships between marketing, beliefs and behaviors, and the following are the questions that we're trying to address in this particular section. How do consumers perceive menthol cigarettes? Do consumers perceive them as safer or less harmful than non-menthol cigarettes?

Do consumers perceive other attributes of menthol cigarettes that imply less harm, such as lower strength, less addictive, more pleasurable, et cetera? Do messages of cooling sensation, refreshing taste, play a role in making the product more palatable to initiators, particularly among youth?

Is there any evidence to show that specific beliefs, such as being soothing, about menthol lead to the uptake of these cigarettes? To what extent is prevalence related to marketing of target populations? What are the direct and indirect effects of menthol marketing on smoking?

Is there any evidence to show that marketing, in consumer perception, affect beliefs about quitting, the likelihood of trying to quit, or cessation?

So those are the questions that we would like to address under the marketing section

The next big section is looking at the effects on initiation and experimentation. And the primary --

DR. SAMET: Dorothy, I wonder, there's a lot here. Should we do it in segments?

DR. HATSUKAMI: Sure. That's a good idea.

DR. SAMET: Maybe start with the marketing, I think, just because there's so much you went over, and then I know we will go through more.

DR. HATSUKAMI: Yes.

DR. SAMET: So if that's okay, I think let me suggest that we break it here for purposes of discussion. Let me open things up. So let's focus first on the marketing.

DR. HATSUKAMI: I would rely on Melanie to answer questions.

DR. SAMET: Jack?

DR. HENNINGFIELD: I think, in this section, it'll be important to recognize that there have been at least three other expert reports in the last year, addressing the general topic of marketing, attractiveness of tobacco products, and how that interacts with physiological effects of products and addictiveness. And that's the European Union's Scientific Committee on Emerging

and Newly Identified Health Risks, 2010; the Framework Convention's Conference of Parties, a European Union and Canadian coalition. And both of those have also touched on menthol. And then, the conference that Dorothy Hatsukami and a number of us worked on, that SRNT, and CPD, and NIH supported, or were involved in.

But it goes right to the heart of some of these issues, and that's how does messaging and marketing build on physiological effects. And so, this is a case where this chapter may be drawing on chapters 3 and 4 as well, because you're talking about physiological effects that are real. It's not an inert substance, where there wouldn't be something to talk about, but, then, how the message is carried forth.

So it's a really interesting challenge because it brings together so many areas that are relevant, but I think that's important in this.

DR. WAKEFIELD: Yes. I agree, Jack. I mean, I think it's important to – this part of the chapter, we'll really try and explain how marketing

of tobacco and marketing of menthol, I guess, creates some expectations about what consumers might experience when they smoke a cigarette, as much as creating an image about the brand itself as well.

DR. HATSUKAMI: I think it'll be really nice to integrate that section with some of the findings that Neal will be coming forth with.

DR. HENNINGFIELD: One more thing when you're going forward, we're addressing concerns, concerns about menthol. Others have addressed concerns about what would happen if there was a ban on menthol. But the point is that there are concerns.

One concern that I have is I'm wondering to what degree is our stalled smoking prevalence in adults accounted for by the rise of menthol use? I'm not sure if we can definitively resolve that, but if you think about it, to drive smoking prevalence down 1 percent, would that have occurred but for increased menthol marketing and uptake?

I think that needs to be addressed, whether

or not we can resolve the issue, because it seems like a very important, legitimate concern about menthol. And conversely, if menthol cigarettes and marketing and/or were not allowed, would that contribute to decreased national prevalence? So hereto, the intersection between this chapter and chapter 4, I think will be important.

DR. SAMET: Neal?

DR. BENOWITZ: To follow up on what Jack said, are there any data, longitudinally, either on marketing expenditures or sources of marketing versus the market share of menthol versus regular cigarettes? I think it would be interesting to try to figure out why the menthol brands have grown so much in the last 10 or 15 years, and see if there's a way to correlate that with marketing efforts or things like that. I don't know what's available.

DR. WAKEFIELD: Well, the industry presented some data to us in July on some of their marketing methods and so forth. So we'll certainly be looking at that and including some of that in the chapter.

DR. BENOWITZ: But, again, if there's something that can follow this over a number of years, and we can try to track for as far back as is available, that'd be great.

DR. WAKEFIELD: Okay.

DR. SAMET: Dan?

DR. HECK: I'm not recalling the specifics. I do recall that there was some presentations on that topic, generally. But let us recall, though, that contemporary marketing and marketing going forward is really the primary focus here. I think that there is a place for scholarly review of historical practices and things like that. But I think we'll have the most valuable analysis here if we focus on the contemporary practice and the practices going forward, which are relevant to the FDA's regulatory authority.

Let's also recall that the overall sales of cigarettes, generally, is indeed in decline, as is the sales volume of menthol cigarettes, that there are some differences in that rate of decline, as we saw from some of the graphics. But I think those

will be important things to bear in mind in the analysis.

DR. SAMET: So I guess I had some somewhat muddled thoughts about the role of history. I mean, we just saw in chapter 4 -- and I think there's this discussion, the need to connect these, that, in fact, there's a remarkable heterogeneity in the prevalence of menthol smoking that we know has historical origins.

So the question of "targeting" historically seems somewhat moot. I mean, we know that there is a historical record of what has been done. I think, with reference to the present, I guess the questions, in a sense, are different because there's a historical pattern that is developed, and then I think the question of whether marketing has maintained that, contributed to sustaining it, becomes somewhat critical.

I think this goes back to what Dan was alluding to. The question of how this happened may be useful. And I think the question of whether there is further targeting going on for other

particular subgroups beyond African-Americans is something you have here as a focus. So, in a sense, there's, in a way, two questions around targeting. One is, does targeting maintain established patterns of the market? And, second, is there targeting that might create new segments of the market?

So I think that we probably need to have some sharpness around what I think is a distinction that may be useful and prudent, so the retrospective look versus the prospective look, and the role of what's going on now, if that makes sense.

DR. HATSUKAMI: Yes. And I think the intention is doing that, because we do see a shift in terms of the type of marketing that they had done in the past versus currently. So we're very sensitive to that.

But I guess the question is whether those help "reassurance," the type of messages that were conveyed many years ago, whether there's still that type of perception, even though the marketing isn't

really focused on doing that. So I think we are aware of the differences between past and current, and we'll take that into account.

DR. SAMET: Jack?

DR. HENNINGFIELD: Even though we're going forward, the historical practices, I think, are highly relevant, though. And this chapter -- there are a lot of challenges here. And one of them is that there are some things that seem obvious, but it may be hard to find scientific studies. And I think that's where probably FDA benefits from an expert group drawing opinions.

Something that seems pretty obvious is, you have -- what are the numbers? 40, $50 million spent for a day on cigarette marketing and advertising? I'm not sure what fraction for menthol. But that has to have some kind of effect. It's a fact that smoking prevalence has been stalled around 20 percent. Would we be at 17 or 18 percent if there wasn't menthol marketing?

I don't know that there is any way to definitively answer that, but I don't think we can

say that it's unlikely that there hasn't been an effect. I'm not sure how we handle that in a report. But to not comment on something like that would seem to be missing the forest, by focusing only on the trees.

DR. WAKEFIELD: Yes. I think it's important that this chapter, this part of the chapter introduce marketing methods and principles as they relate to tobacco. And there's good expert reports on that available as well, to draw from. So I think some of it might be stating the obvious. But I think in the context of what we're trying to do here, it's really important to include. I agree.

DR. HENNINGFIELD: Yes, in that context. By the way, I mentioned -- it's kind of here in other reports -- but NCI monograph -- is it 19, Melanie, that you and Ron Davis -- is highly relevant here, it seems to me.

DR. SAMET: Yes, Cathy?

DR. BACKINGER: To confirm what Jack said, I mean, I think the historical context is really important. And you may not want to spend a lot of

time on it, but it is important. And this kind of then bleeds over into the next section. So I guess there's a reason why these are together, because the marketing obviously impacts initiation and cessation. But also, the marketing impacts social norms, peer influences, parental influences.

So while the marketing tactics may have changed, you have parents, peers, using products that then influence initiation. So I'm glad to see that consumer perception piece in there, and I know we haven't gotten to the other sections, but consumer perception is going to be important, I think, in all of the areas.

DR. SAMET: Mark?

DR. CLANTON: This issue of consumer perception is normally aggregated into what we would call brand or brand experience. And we're starting to talk about that as well. There's probably some data about brand perception, but a lot of it's going to be probably vetted by expert opinion and view.

But brand experience is very complex and

contains hundreds, if not more, variables, some of them related to fact and some related purely to myth, that may be propagated through social networks. And that happens with children and it happens with adolescents all the time. Myth is often transmitted as a matter of fact through social communication and social networks.

But it all ends up in brand, which is, what does engaging in this activity do for me? How does it cause other people to think about me? What do I get from this experience, in terms of utility, multiple utilities? And I don't know that we've figured out yet how to explore brand and brand experience, but it's always more than physiology. It's always more than current marketing practices. It's always more than any single variable. And if we can begin to -- the way I articulate it is -- unpack brand and brand experience, we'll understand the complexity of how brand, branding and brand experience impacts demand and sales.

DR. SAMET: Okay. Dorothy? Nothing?

Other comments about the marketing segment?

Yes, Dan?

DR. HECK: Yes. Just briefly to Mark's comment, I think we are fortunate. I believe it's the NSDUH survey. We do have at least some direct questions on consumer perceptions of menthol cigarettes and non-menthol cigarettes, generally among smokers, as well as by racial or ethnographic subpopulation. So we do have a resource for information on consumer perceptions of perceived harm from that survey.

DR. SAMET: Okay. Any other comments on the marketing segment?

[No. response.]

DR. SAMET: Next segment.

DR. HATSUKAMI: Okay. Thank you.

So the next segment is on initiation and experimentation. And the primary questions that we are asking in this section are the following. Does access -- and now it's changed to "availability" -- to menthol cigarettes increase the likelihood of experimentation? I guess that's just one question.

So under this section, these are the

questions that we're trying to answer. And we're focusing on youth as well as young adults because that's when experimentation and initiation often occur.

What is the prevalence of menthol and non-menthol cigarettes smoking among youth or experimenters by racial, ethnic group, currently and over time, compared to other age groups? So for this question, what we're trying to look at is the whole issue of age gradient. And we're looking at age gradient, not only across the youth and in older adults. We're also looking at the age gradient within youth, so middle school versus high school.

We also are interested in looking at what types of cigarettes youth like to smoke and young adults like to smoke, and seeing what the trends are in terms of their preference for different brands of menthol cigarettes, and looking at what the content of menthol and nicotine are in these cigarettes in determining whether the content has changed over time.

Another question that we're trying to answer is, is there a higher prevalence of menthol cigarette use among more recent youth, young adult smokers, compared to more established youth adult smokers?

Thirdly, what is the pattern of switching among this population? What is the extent to which smokers who initiated smoking with menthol switch to menthol cigarettes, and what is the extent to which non-menthol smokers switch to menthol cigarettes?

Some other questions that we're asking in this section, is there evidence to show that there is an earlier age of initiation? Does menthol make cigarettes more tolerable for inexperienced smokers, thereby increasing the likelihood of experimentation? And what other influences exist in the use of menthol cigarettes among initiators?

Do beliefs or perception about menthol among peer groups or parents -- so this is where, Cathy, your questioning comes in -- affect the initiation of smoking menthol cigarettes?

Do you want me to go onto the other?

DR. SAMET: Yes. I think that would make sense. So we'll sort of go through this with experimentation now. Yes, Neal?

DR. BENOWITZ: How are you going to define experimentation?

DR. HATSUKAMI: Well, that's a good question. So you can define it in a couple of ways. One is to look at people who used less than 100 cigarettes during their lifetime. So that might be one way. Another way is to take a look at the number of cigarettes or occasions they smoked cigarettes. So you can say, okay, individuals that smoked less than 1 to 5 cigarettes a day, 5 to 10. And I guess another way would be to take a look at individuals that smoke some days versus every day. So there are different ways to define experimentation.

DR. BENOWITZ: Yes. I think it's going to be important to separate out the trial of the first few cigarettes --

DR. HATSUKAMI: Yes.

DR. BENOWITZ: -- which is, you'll know if someone goes beyond three or four cigarettes, then their chances of becoming a smoker are important, but a lot of people stop after the first two or three.

DR. HATSUKAMI: Right.

DR. BENOWITZ: Where the aversive or where the pressure to smoke overcomes the aversiveness, I think that's a key point.

DR. HATSUKAMI: Yes. And that's really difficult to find that literature, to take a look at people that just smoked one or two and then didn't go beyond that. But that's good.

DR. BENOWITZ: Then I think the second part of it, which you could call occasional smoking, is when kids are smoking on Friday night, at a party, or something, but don't smoke on a regular basis. And some kids stay there and quit and some kids progress. I'm not sure that's still experimentation; that may be called something different. But that is also an important thing to look at, how they progress from occasional smoking

to becoming a daily smoker.

DR. HATSUKAMI: Right, yes, and we do that in the next section.

DR. SAMET: It seems like at least one of your goals is, does menthol make cigarettes more tolerable? I think that goes back a bit to chapter 3. So I guess the question I would ask is, how would you propose to address that question, let's say beyond the kinds of materials that Neal would be reviewing in chapter 3?

DR. HATSUKAMI: We would primarily look at the studies that looked at youth initial experiences with menthol cigarettes and what their reports were of that initial experience. Unfortunately, there isn't really a lot of literature in that area, but that's really important to point out as well. But we'll take a look at that literature.

DR. SAMET: Yes, Cathy?

DR. BACKINGER: Just following up on that specific one -- and I don't know much about this area. But I know that in the special issue of

Addiction – and Dr. Fagan's paper referenced a paper about African-Americans being super tasters. And I think that could be -- I'm not sure whether it fits in with chapter 3 or here, but I think looking at some of the sensory processes and taste sensation could affect initiation, particularly in African-Americans. So you could look at her paper to find that reference.

DR. HATSUKAMI: That's a good point.

DR. SAMET: Okay. Experimentation, onward. Dan, sorry.

DR. HECK: I was just going to say earlier, I do share Dr. Hatsukami's perception that the scientific information in this area is really thin. The only paper I'm aware of or have been able to find in this area is the DiFranza 2004 paper.

As far as I'm aware, that's the only literature available directly addressing this initiating, experimentation cigarette phase versus early brand preference. So it's, I think, an area where we do need some additional information.

DR. HATSUKAMI: Okay. We'll go onto the

next primary question, which is the following. Does – and now its changed to "availability" of menthol cigarettes increase the likelihood of becoming addicted? And does inclusion of menthol in cigarettes increase the degree of addiction to the smoker?

So to address these particular questions, we'll be looking at the abuse liability data, the likelihood of becoming addicted, as well as looking at the extent of addiction. In terms of the area of abuse liability, unfortunately, there isn't really that much literature in this particular area. But we felt that it would be important to emphasize that, that there are some research gaps. But what we'd like to deal with in this particular section are the following questions.

Is there evidence to show menthol alters level of MTK of nicotine to make menthol cigarettes more addictive? And I guess, Neal, you're covering some of this already in your section. So I'm not sure if we could probably exclude it in this section.

Is there evidence through animal and human studies to show that menthol cigarettes, menthol in cigarettes enhances the abuse liability of nicotine/cigarettes?

Is there evidence to show that youth experimenters, that is, youth smoking less than 100 cigarettes in a lifetime, respond to menthol cigarettes differently compared to non-menthol cigarettes? What are moderating factors, such as age, racial, ethnic groups, to these responses? And, again, there isn't really that much literature in this particular area.

In terms of the likelihood of regular smoking and addiction, these are the questions we'll address. Are smokers who experiment with menthol compared to non-menthol cigarettes more likely to become regular smokers? Are they more likely to become addicted smokers? For example, are those who begin smoking with menthol cigarettes more likely to continue smoking than those who initiate smoking with non-menthol cigarettes?

Do menthol smokers experience more rapid

trajectory towards regular smoking or addiction compared to non-menthol smokers? And this is where we don't have that much literature, unfortunately.

Do menthol compared to non-menthol cigarette initiators tend to be a population more vulnerable to addiction? And this would dovetail with some of the information that you'll be getting, Karen and Patricia. So those are the questions that we're asking in that particular section.

Then, finally, the extent of addiction; these are the questions that we're trying to address. Do menthol versus non-menthol cigarette smokers differ in cigarettes per day, exposure to nicotine, levels of cotinine, cotinine per cigarette? That is, is there evidence to show that smokers experience greater levels of nicotine from smoking menthol versus non-menthol cigarettes? And then, is there any evidence to show that menthol smokers are more dependent than non-menthol smokers as assessed by different measures of dependence. And they include the measure that we'll be looking at, including the FTND, time to first cigarette,

waking up in the middle of the night to smoke, as well as the experience of withdrawal symptoms.

So that's the section on likelihood of addiction and extent of addiction.

DR. SAMET: Okay. Thanks.

Jack?

DR. HENNINGFIELD: You have a lot of work to do.

[Laughter.]

DR. HATSUKAMI: Yes.

DR. HENNINGFIELD: This is another area where, if we focus too much on the narrow questions, we can miss things. For example, you and I both do abuse liability work, and that's relevant and important. But I think this is a case where we're going to have to look at precedence and what we can learn with other substances and products.

Two of them that are of classic importance, one is crack cocaine, and one of the classic papers, Dr. Hatsukami and Fishman wrote. But the crack formulation did not make cocaine more

addictive or increase the abuse liability, but it made it easier to experience, repetitively, the addictive effects. And there's no question that that formulation drastically increased cocaine addiction and health consequences. Similarly, the OxyContin formulation of oxycodone didn't make it more addictive. It made it easier to experience the addictive effects and more attractive for a lot of people. So the formulation, then, had to be addressed.

I think there are a number of examples like that, the alcohol products, sometimes referred to as slickers, put in the gelatin-like solutions, they don't make the alcohol more addictive. They make it easier for young people to easily ingest large quantities of alcohol. I think examples like that, I think, are as relevant as direct, scientific studies.

We had some discussion yesterday. I think Mark Clanton pointed out that if we are limited only to peer-reviewed studies or direct scientific studies, we can miss the obvious. And I think

those are some examples where there are some obvious historical lessons in the literature.

DR. HATSUKAMI: Yes. I think you're right, Jack. And I think, also, one area that we're going to be targeting is looking at the relationship between sensor cues and addiction.

DR. HENNINGFIELD: Yes.

DR. HATSUKAMI: So the importance of associated sensory cues with nicotine, I think, would be relevant literature.

DR. BENOWITZ: One thing we talked about yesterday I think that's important in talking about addiction is in relation to the number of cigarettes per day. We talked about the fact that there is evidence that African-American smokers are more highly addicted, despite smoking fewer cigarettes, by several criteria, and I think that's an important issue. It's not just addiction per se, but in relation to smoking behaviors. So as much as we can include about that, I think that's important.

DR. SAMET: Dorothy, can you go back to the

abuse liability slide? One of them was abuse liability. So this is just, perhaps, my naivete in this area, but when you say that youth experimenters respond to menthol cigarettes differently, what would be the indicators of different? I mean, what kinds of things would you be looking for there?

DR. HATSUKAMI: So again, there's hardly any literature on this, but we thought it would be an interesting question to pose, to see whether there might be anything. But it would be, like, is there more greater satisfaction, more pleasure, feeling more dizzy and high, so on and so forth. So those are the kinds of responses that we were looking for in studies, and there aren't very many of them.

DR. SAMET: Yes, Corinne?

DR. HUSTEN: Yes. I just had a clarifying question to expand on what Neal was saying. So for the dependence measures, because of the differential metabolism of nicotine by race, are you planning on restricting the studies to those that are within a racial ethnic group or that

stratify by race?

DR. HATSUKAMI: Yes. We'll be looking at stratification by race and also by age. So we will be taking a look at that because, obviously, when you're young, too, it may affect the number of cigarettes you smoke, for example, because some of the teens not being very comfortable smoking in certain situations.

So we'll be looking at that, as well as looking at the measures themselves; are they reflective -- to what extent are they reflective of dependence. And then are there some confounding factors that might affect the response to these dependence measures. So we'll be taking a look at that.

DR. SAMET: Neal?

DR. BENOWITZ: I wonder, since there's such a high correlation between racial ethnic groups and menthol use, if we need to have a few paragraphs talking about biological differences that have been observed in smoking behavior and genetics, by racial group, because we know that nicotine

metabolism, on average, is slower in African-Americans. It's slower in Asians, Alaskan Natives. There's also some evidence there. And smoking behavior is different in terms of cigarettes per day.

So I wonder if we need a section somewhere -- I'm not sure where it should go -- basically on racial ethnic differences, and smoking behavior, and metabolism, because that's important to understand the menthol in that context. I'm not sure where it should go.

DR. HATSUKAMI: Yes.

DR. SAMET: Chapter 3?

DR. HATSUKAMI: I think in your chapter, Neal, not in this one.

[Laughter.]

DR. BENOWITZ: I have no problem with that. But I would be happy to write it, but I don't think it's in chapter 3 because it's not menthol pharmacology. So I would be happy to write it for some chapter.

DR. HATSUKAMI: Yes. I mean, we certainly

can write something to that effect, although we are taking a look at information within ethnic groups, too, so looking at dependence within ethnic groups that might --

DR. BENOWITZ: I think this explains why it's important to do that.

DR. HATSUKAMI: Yes, yes. That's right.

DR. BENOWITZ: So we just need to figure out, Jon, where it goes.

DR. SAMET: Yes, Mark?

DR. CLANTON: Yes. I'm not sure where it goes either, but I do think it needs to be in there. I'll take a shot at drafting it, and then we can figure out where to plug it in at that point. I think this is another topic that can easily finds its way into a number of chapters. But I do think we need to look at what's available in the literature on biological differences.

There are data that look at nicotine receptor affinity and things like metabolism, cytochrome, metabolism of nicotine, based on racial groups. Don't know how much ethnic data there is,

but we can take a shot. I'll take a shot at drafting it, and then we'll figure out where to plug it in.

DR. SAMET: Yes, Susan?

DR. KAROL: Just from the Native American standpoint, we have a lot of data from our epicenter that we would be happy to include for you if you need it.

DR. SAMET: Okay. Anything else on smoking, addiction, abuse liability?

[No response.]

DR. SAMET: Onward. You've still got more work.

DR. HATSUKAMI: Okay. So should we go onto the next section, a section which is the last one? Thank goodness. And that's on the topic of cessation. And the primary question is the following. Are smokers of menthol cigarettes less likely to quit successfully than smokers of non-menthol cigarettes? So we're going to take a look at the likelihood of cessation, as well as mediators of cessation.

In terms of the likelihood of cessation by mentholation, we're asking the following questions. What is the evidence that menthol cigarettes decreases cessation in general, and by age, and by racial ethnic groups? And we'll take a look at a number of different types of studies. Actually, with the other sections, we'll be looking at all these different types of studies as well. But they include the epidemiological studies, the longitudinal cohort studies, cessation treatment studies, and any other types of studies that we deem relevant.

The other question that we thought would be important to address is if there's any evidence to demonstrate that certain treatments are less effective among menthol smokers compared to non-menthol smokers? And in terms of mediators of cessation, this is related to what Melanie and Lisa are going to be writing; is there any evidence to show that sensory effects from menthol affect cessation? And then, secondly, how does target marketing special populations affect rates of

cessation? That is, menthol cigarette use is highest among youth, females, African-Americans and lower SES. Do these groups experience health disparities because of less access to treatment or less willingness to seek treatment? And are these groups, in general, more likely to fail at smoking cessation?

So those are the questions that we're dealing with in the cessation area.

DR. SAMET: Okay. Neal?

DR. BENOWITZ: I've got two suggestions. One is when you're talking about cessation, I have to talk about what measures. We can look at total former smokers. We can look at lifetime cessation. And I also think we need to look at cessation as a function of quit attempts because those are different parameters.

Then the other thing is just that I'm curious in the very last slide, when you're talking about sensory effects. Is there evidence to show that sensory effects of menthol affect cessation, or are you talking about like cues from menthol

foods making somebody relapse to smoking cigarettes? Or what exactly do you mean by sensory effects on cessation?

DR. HATSUKAMI: I think that's a really good question. Yes. I think there's some animal literature that shows that if you have certain cues that are associated with nicotine, you're less likely to extinguish, compared to just nicotine alone. So there isn't a lot of literature in this particular area with regards to menthol, but I think we can tap into some of the areas regarding abuse liability to see how that might potentially affect cessation.

DR. WAKEFIELD: Dorothy, here, I think we were also going to include the likelihood of making a quit attempt, as well.

DR. HATSUKAMI: Yes.

DR. BENOWITZ: But I don't understand exactly. What do you mean by how the sensory effects would influence the likelihood of a quit attempt? What do you mean by that?

DR. WAKEFIELD: So that issue of, you know,

whether or not the cooling sensations and so forth might make people less likely to think they need to quit smoking, and to try to quit in the first place, or might make them more confident that they could quit smoking if ever they needed to, and so forth.

So it's the whole constellation of quitting-related beliefs, intentions, and behaviors. I think it's important to look at the whole set together.

DR. HATSUKAMI: Yes. And also, the fact of the beliefs -- it's not just the cooling, but what are their beliefs about it? Do they have health beliefs that they think that they are smoking a less hazardous cigarette, and might that perpetuate continued use of menthol cigarettes.

DR. SAMET: Dorothy, the bullet, is there any evidence to demonstrate that certain treatments are less effective among menthol smokers, by certain treatments, do you mean cessation, or do you mean anything else?

DR. HATSUKAMI: I'm mostly focusing on

pharmacological treatments here, are they less responsive to the pharmacological treatments; primarily, because that's where the literature is.

DR. SAMET: Okay.

Other questions about cessation? Comments?

[No response.]

DR. SAMET: So I had one question I was thinking about in the discussion about the historical context and marketing. There are historians. I guess a person who comes to mind who has done some study on this is Robert Proctor. I mean, do we want any input from a historian or is this sufficiently minor, that you will be able to look at the issue on your own?

DR. HATSUKAMI: Melanie?

DR. WAKEFIELD: I think we can look at it on our own. I think it's fine.

DR. SAMET: Okay. And then anything else on this book of a chapter?

DR. BACKINGER: Well, I had one question.

DR. SAMET: Yes, Cathy?

DR. BACKINGER: I'm not sure if it's

appropriate for this chapter or somewhere else, but I guess I think I asked this at a previous meeting. Is there going to be a place where, objectively, you're going to look -- not just this chapter, but all the chapters -- at the available data, published literature, but making any kind of recommendation or thinking about what's more important in the scheme of things?

So is it more important that menthol smokers are less likely to quit, more likely, or the same versus initiation versus the physiological impact of menthol? And I'm just trying to get a sense of, are you going to address that?

DR. SAMET: Why don't you hold the thought until we come to chapter 7.

DR. BACKINGER: Okay.

DR. SAMET: I think we'll have some discussion of what I think is an important issue that you're raising.

DR. BACKINGER: Thank you.

DR. SAMET: Yes. Let's see. Anything else on chapter 5? So that leaves us with 6 to discuss,

which will probably take at least a minute, and 7, which will take longer. I think it's probably a reasonable time for a break. But I would like to sort of just get a calibration so we can decide on when we think we might end.

Does noon seem roughly right? We know we're losing Karen at 11:00 and Dorothy not soon thereafter, I guess. So I think if we said that we would be done by noon, I think that gives us a chance, an opportunity, to discuss 6, 7, I think take a look at our discussion questions, because I do want to make sure we circle back to David Mendez and what we heard yesterday, and some of those, what we may need to provide him.

So I think probably noon is a reasonable time to think about going. If it sums up okay for Mark, then that's it. Okay.

So let's break until 10:00.

(Whereupon, a recess was taken.)

DR. SAMET: Okay. Why don't we go ahead and get started again? So we're back. We've discussed chapters 3, 4, and 5. And a lot of hard work has

been done on chapters 3, 4, and 5. I say that as preamble to chapters 6 and 7, which we're going to get started on.

Chapter 6 – Risk Factors

Jonathan Samet

DR. SAMET: So chapter 6 is the chapter on risks to smokers of menthol versus non-menthol cigarettes. And to be involved in this will be Neal, Mark, and myself. And I think, at this point, we have created four bullets, which are on the next slide. It's such a brief presentation. We created four bullets and that's it. It had some discussion about how we're going to proceed. And I think, unlike chapter 5, it's a much more constrained body of literature to review.

Some of it has already been identified. For example, we're aware of a relatively limited body of epidemiological studies that make direct comparisons of the risks of smoking menthol to non-menthol cigarettes. There's literature on biomarkers. Dorothy already mentioned that chapter 5 will cover the literature on nicotine and

cotinine. And I'll leave Neal to discuss a little bit about other biomarkers that will be considered.

There are a number of studies on smoking topography in relationship to menthol versus non-menthol and some body of toxicological studies that I will take on. So I think once we get over some of the work on some of the more difficult chapters, particularly, I want to get chapters 1, 2 completely finished. Then we'll be turning our attention to these studies. I think our efforts in some of the areas will be to use a systematic-review approach, capturing all the relevant studies in epidemiology, for example, or likely topography. For biomarkers, I think the review will be somewhat more selective, focusing on selected biomarkers. And the tox, again, we'll try and identify all studies.

So, Neal, do what I had on the biomarker story.

DR. BENOWITZ: There's not much to say. I think there are four or five studies now that have looked at various biomarkers in people smoking

mentholated versus non-mentholated cigarettes, which we'll summarize. An important question, and one that I'm not sure how much data we can analyze, is cigarette smoking levels versus biomarkers. It's a big question.

One question is whether, in general, are menthol smokers exposed to different amounts of biomarkers compared to non-menthol smokers? The other issue is, is exposure different as a function of how many cigarettes you're smoking per day? And that's something that I'd like to look at, but I'm not sure we can find that data.

DR. SAMET: Okay. So Mark?

DR. BENOWITZ: I'm sorry, Jon. But one thing is, we might want to make sure this chapter talks about direct health risks because risks in general, we're going to be looking at the risks of smoking a mentholated versus a non-mentholated cigarette. But we're not saying are there more mentholated cigarette smokers, because that's another risk of menthol. It's not going to be addressed in this chapter.

DR. SAMET: Correct.

DR. CLANTON: Correct.

DR. BENOWITZ: So that's really direct health risks.

DR. SAMET: That's right. So this other matter that you talked about is chapter 7.

DR. BENOWITZ: Right.

DR. SAMET: Mark?

DR. CLANTON: Given the sheer number of biomarkers that have been studied, I wonder, in addition to just describing what they are and how many there are, is there any way of beginning to sort through them; for example, trying to find the cholesterol marker that gives us clear information about cardiac disease, or a biomarker that presents us with some clear physiologic effects.

Is there a way of sorting through that, or is that just a huge mass of information on the number of markers there are?

DR. BENOWITZ: Well, it's been hard to validate specific biomarkers versus specific diseases. We know that there are associations, for

example, the association between urine and NNAL in lung cancer risk. But, of course, urine and NNAL is highly correlated with pHs, and with everything else is tobacco smoke.

So we can basically say the number of carcinogen-type biomarkers or some oxidant stress, potentially cardiovascular biomarkers, we can classify them, but none has been specifically validated, partly because they all go together. All the toxins are highly correlated with one another in tobacco smoke.

DR. CLANTON: For example, the biomarkers that are associated with DNA damage -- and you mentioned those first -- is their way of, again, trying to impute some sort of priority in the various lists and categories of biomarkers?

Again, I would assume that biomarkers that cause DNA damage or disruption, which is critical to carcinogenesis, might be weighted more heavily or more important than other kinds of cotinine, for example, as a biomarker. And I don't know that there is an answer, but I'm just wondering is there

a way to sort through that in any fashion.

DR. BENOWITZ: I don't think there is. We will certainly mention what the biomarkers are potential biomarkers of. But, again, the problem with anything in trying to separate out biomarkers is that they all are very highly intercorrelated.

DR. SAMET: Other comments about chapter 6?

[No response.]

DR. SAMET: Okay. Brief chapter presentation, brief discussion.

Mark, we'll move to chapter 7.

Chapter 7 – Public Health Impact

Mark Clanton

DR. CLANTON: Okay. These are the principal participants to date; however, we'll draw a great deal of information from the other chapters in writing the chapter on public health impact. The overall purpose of this chapter is to describe the impact or the public health impact of the use of menthol on, certainly, the general public, as well as specific groups.

We're probably going to create a symmetrical

presentation, where we're going to look at the impact of menthol cigarettes on individuals from a health perspective, and then also summarize the evidence and data on populations, and then stratify, based on the evidence, those populations into the groups that we're required to look at, such as children, African-Americans, Hispanics, and racial and ethnic minorities.

Going back to Section 907, even though the previous chapter, chapter 6, specifically has been asked to look at risks, I want to make that point that chapter 7 is where we're going to summarize and synthesize all of the conclusions and all of the evidence from the previous chapters.

There are only two sections here that I think are going to be original, if you will, that most of the outline of chapter 7 is going to draw from what we learn in marketing, from what we learn in patterns of menthol use, from the chapters on biomarkers, and et cetera.

So this is, in large measure, a synthetic piece. And this outline is going to change based

on what we begin to get as drafts from the other sections. But our focus is to make sure that we've answered specific questions related to risks and benefits to the population of removing menthol or enacting some sort of menthol ban.

The method, of course, as I just described that, is to summarize previous evidence and data from the previous chapters. And we're going to be looking at the models that might be used in previous chapters as well, maybe to try to do some projections on what will happen to health at the individual level, the public health level, and potentially model the effect of some non-health related events that could happen as a result of contraband, for example. By the way, your slides do not precisely reflect this because this was changed based on yesterday's discussion. So this will be available to you in its edited and changed form.

Methods, we'll review models useful for estimating and projecting the effect of a ban on potential change rates of smoking initiation,

smoking prevalence, and smoking cessation rates. We will decide whether or not those things that are modeled end up primarily in their original chapter, or whether they're represented here. If they appear in previous chapters, again, we'll try to summarize and clarify the conclusions that come from those previous chapters, looking at the models we decide to use. We're going to prepare model projections of disease burden, smoking initiation prevalence in menthol and in a menthol ban state versus the current state of menthol use.

There are a set of questions that were outlined in chapters 1 and 2. I've brought them back here to make it clear that it's in chapter 7 where we make sure as best we can that we've answered those questions, either in previous deliberations or maybe in some original language here. But we're going to look at questions related to individual smokers and questions related to smoking at a population level. I'll go through this quickly because, again, we presented these questions in chapters 1 and 2.

The questions that are relevant to be answered to individuals -- does access -- and I think we've changed that to "availability" now.

Does availability of menthol cigarettes increase the likelihood of experimentation? Does access or availability to menthol cigarettes increase the likelihood of becoming a regular smoker? And does inclusion of menthol in cigarettes increase the likelihood of smokers becoming addicted?

Lastly, does inclusion of menthol in cigarettes increase the degree of addiction of smokers? Again, we'll either summarize the answers to these questions or provide original answers. Again, 5, 6, and 7 are as stated in the chapters 1 and 2.

Smoking at the population level, the questions that are relevant there -- again, does the availability of menthol cigarettes increase the prevalence of smoking in the population? A lot of this will be drawn from the very comprehensive discussion of marketing that you heard in Dorothy's

chapter. Number 2, does tobacco company marketing of menthol increase the prevalence of smoking beyond anticipated prevalence, if these cigarettes were not available?

Again, we're repeating these questions, but the point here is that the answer must come to these questions clearly in chapter 7, and we'll sort out exactly how we do that.

We'll draw heavily from the patterns of menthol use because, normally, if we would describe the public health impact of anything, any chronic disease state, or any exposure, the two things we put together are the epidemiology, the incidence and prevalence of the exposure, and then the incidence and prevalence of the effect, in this case, chronic disease. So, again, we're going to make sure that we answer those questions here as clearly as possible.

This section is actually an original section, if you will. It's not just derivative, necessarily, of a previous discussion. We'll try to look for the evidence, explore the evidence, and

present the evidence in a comparative way that looks at health and indices of health status in menthol versus non-menthol smokers.

These are only a couple of examples of potential differences you will find in menthol versus non-menthol smokers. So in overall health status, there may be differences in body mass, in blood pressure. These are not diseases, per se, but are surrogates for chronic disease such as cardiovascular disease, diabetes, and cancer. And so, again, we'll explore whatever evidence and data is available there by comparing menthol smokers versus non. We're also going to look at mortality to see if there's any data that tells us if there's any difference in mortality rate.

Let me make one point that we've alluded to throughout these discussions, which is there may be no data or good peer review data to describe some of these things, but we still have an opportunity to talk about the studies that should be done and areas that need to be clarified or elucidated. So wherever there are data, we'll present them. And

where there aren't data, we'll talk about recommendations where that should be collected through future research.

This is a new section. It's not just derivative of previous sections. This is an attempt to project what will happen to the public health, based on removing menthol from the market. We want to understand what happens to youth initiation, and certainly initiation overall, and what might happen on overall smoking prevalence. We did have presentations from our University of Chicago economists and some other presentations that give us an idea what might happen in a ban. But in this section, we'll look at whatever models tell us and try to make projections on what'll happen to the general population, children, racial, and ethnic populations.

Of course, we'll attempt to model, if there's time, to get the data and model it. What will happen as it relates to the demand for smoking cessation services? I think that's been brought up, potentially, by one of our industry

representatives, that we need to understand what will happen if there's a ban as it relates to the availability and access, and potentially cost, even, of smoking cessation services. So if we can model that, we'd like to model that.

The potential effects of removing menthol on the market, as it relates to contraband, this is not a derivative summary section. This is a section on its own. We've been actually asked, I believe, by Section 907, to specifically address contraband. So we will take, certainly, our presentations from yesterday and other evidence from the literature to try to understand what we think might happen to menthol cigarettes if, in fact, there is a ban or a removal of menthol from the market, and try to anticipate what will happen. Again, these are derivative. These are taken directly from yesterday's presentations.

We may be able to add a few topics in this area. But I think we'd like to be able to understand what we think will happen if, in fact, there are black market activities and alternate

access or production of menthol and mentholated cigarettes.

Chapter 6 is, again, about risks and potential -- more about risk, but we'll try to summarize anything we can about risk and benefits of removing menthol from the market and stratify that by individuals, populations, and special groups. Racial and ethnic groups, children are specifically outlined in Section 907, so we'll address that here.

So on one hand, it's sort of unsatisfying because a lot of this is going to be derivative of other areas. On the other hand, this is where the rubber meets the road. It will be in this chapter that we clearly describe what risks there are, what potential impact, external and predictable impacts there might be in removing menthol from the market, and also try to understand what is the differential health status or impact between menthol smokers and non-menthol smokers.

I suspect, Mr. Chairman, this is going to change, even as we go forward with the other

chapters.

DR. SAMET: Thank you. Thank you, Mark. And I think we understand that this builds on things, building blocks that are only partially in place. And I think critical for us will be our interactions in future meetings and constructing what is obviously a very important chapter.

Just as a comment, I think the model, for example, makes a comparison of the world as it would be if menthol brands would remain, versus a world without menthol brands, if for one reason or another, they were to not be present. That does not necessarily imply that there's a menthol ban. So I think the counter-factual is the sort of non-existence of menthol brands, which might be achieved in one or more ways. So this is a point.

David's model currently builds from a 2010 population. So, for example, if we were going to make estimates of the consequences of removal of menthol brands from the market, he could march forward by however many years we feel are appropriate to describe what might happen in terms

of the various smoking populations and potentially the disease outcomes, which, of course, would be manifest in a different -- some point out in the future, I think; as somebody pointed out, if we find no evidence that risks are different for these products, reflect changes in the number of smokers, rather than, let's say, a change in the relative risk, and a very simple, attributable risk formulation.

So let me open up chapter 7 for discussion.

DR. CLANTON: I just wanted to respond quickly that I do appreciate the difference in modeling a world without versus a world with, as opposed to a ban. So I've made a note, and based on whichever models we select, we'll try to appreciate that difference in the report.

DR. SAMET: Thanks.

Neal?

DR. BENOWITZ: One thing I think we should specify, and we'd probably just draw this from what's coming available, but what would be the criteria for a menthol ban? Like what levels of

menthol? What content of menthol in a cigarette? We need to specify what that means. And we know that lots of cigarettes have got low levels, and we've got to figure out what's a characterizing level.

DR. CLANTON: I think that's not just an interesting question, it's an important question to answer. Ultimately, whether FDA, in receipt of this report, engages that, in other words wants to work through that as a regulatory issue, versus the committee sort of offering that up, I'm not sure where that would sit. I think that's an important question to answer because the essence of the report is asking for, tell us what the impact is. What is the impact of changing the availability of menthol?

So we could actually do that without necessarily coming up with the criteria for actually creating a ban. But, again, I'm not sure whether that would be FDA taking that on in their regulatory discussion or whether we would do that. But I don't know the answer right now.

DR. HENNINGFIELD: We've touched on that topic, and what's interesting, of course, is that most of our population data are on characterized and branded levels versus all other cigarettes, many of which contain menthol. And that doesn't mean that, in regulation, if menthol were recommended to be banned, or marketing, whatever, that the agency couldn't say, well, our approach is to ban all levels.

But I think that in our reports, we have to make clear where the evidence is, to help guide the regulatory approach, because the regulatory approach then has to consider a lot of other things beyond that. That's my own --.

DR. SAMET: Dan, I was going to ask you, in fact, maybe the question you were about to answer. But historically, how long has some menthol been in most cigarettes?

DR. HECK: Well, I think it goes back to Giovino in 2004, the statement from, I believe, the first menthol conference. Menthol is found in greater than 90 percent of cigarettes. I never was

able to find an authoritative reference support for that statement. I think that menthol is a natural constituent of a number of botanicals, most prominent in the peppermint family, so I don't know the answer to that.

But I think since the statute deals with the characterizing levels, which I think we saw from the July meeting, might reasonably be something on the order of 1,000 parts per million, weight-to-weight tobacco, where we would have an ordinary consumer or perhaps an expert taste panelist being able to pick up a menthol-flavored note, in that ballpark, anyway.

I guess I don't know if it's a matter for legal interpretation or whatever, but I guess my reading of the statute referred only to the characterizing levels, which I think in our conventional understanding would be a traditional menthol cigarette. At least, that's my read of it, anyway.

DR. SAMET: Okay. Other comments on chapter 7? Yes, Dan?

DR. HECK: I had one. I guess, particularly the diversity of individual questions and the very complex chapter 5, we had a great number of essentially yes/no questions relating to various aspects or examinations of the effect -- or potential effect of menthol on initiation, cessation, those behaviors.

It was puzzling to me, I guess initially, after seeing the depth and complexity of these yes/no questions, how these yes/no answers, if they're determinable, were going to be integrated into this weight of evidence equipoise concept. We may have some yeses, nos, and maybes. And perhaps, that's the burden of Dr. Clanton's chapter 7, to figure out a way, which I guess is not immediately apparent to me, how these bits of information, consistent, inconsistent, or contrary in some, most instances, can be synthesized or will be synthesized into this equipoise weight of evidence judgment.

Just a passing comment, too, with regard to the, I guess, new information we heard, for

instance, the NCI intent piece, we heard yesterday, am I correct in presuming that any new information provided to the writing committee will be also provided to the stakeholders? And by the same token, any additional stakeholder-held information that needs to be provided to the committee to help them resolve some of these questions we've seen presented -- we'll have to have a good mechanism to achieve that in very rapid time.

DR. SAMET: With regard to, I guess sort of, the transparency of evidence, I mean, I think we stated up front that that was going to be one of our principles. So I would say that with the exception of any commercial confidential material that we would rely on, those documents, datasets, and so on that we use should be there and available.

I think, with regard to other requests for information, I certainly agree that if we needed anything more, it would have to be made rapidly and expeditiously. And I think that I'm not sure that I've heard, as we've gone through the various

chapters, too many areas where we are going to be seeking information on a rapid time frame that we think is going to be critical. I don't think we've heard that across any chapters. I think a lot of evidence has been presented to us.

DR. HATSUKAMI: Yes. For chapter 5, there are some questions that I would like to have maybe FDA try to get some information on, on some of our national datasets. Yes.

DR. SAMET: But, for example, maybe perhaps with regard to Dan's question, requests back to industry are not likely to be fully forthcoming, anyway, that I would anticipate.

DR. HECK: I've been trying to sense -- I thought I heard maybe a little sense around the table. There were some, possibly, minor areas, some little minor refinements, or clarifications, or further information that might be useful. And by the same token, any publicly available information that the committee may be considering as newly appearing, we would want to look at that as well.

DR. SAMET: Corinne?

DR. HUSTEN: This was a point that I was going to make, certainly, before we wrapped up, that if the committee does have other studies that they want us to find, or analyses, to let us know as soon as possible because we do need to make that information available to the committee.

There are restrictions on how fast you can get information and everything. And the report is due relatively soon. But, certainly, anything that the committee's going to rely on in the report, we need to make available to the entire committee. And so, the sooner we know, the more we're able to do that.

DR. SAMET: Then I think just back to what I think was the other query you posed, which was sort of the overall summary and synthesis, we did have our seven plus two questions, our seven individual level and our two. And those are, to an extent, cutting across the chapters. And, certainly, within the proposed classification of strength of evidence – and I think, Mark, you speak to this --

we are anticipating providing answers to those in this chapter, according to a uniform format.

DR. CLANTON: Yes, that's right. And to your earlier point, it's going to be a challenge. There's no question about that, but we'll attempt to do that.

DR. HECK: So our concept -- and I'm asking this because the industry report idea will be to have it consistent with, or complementary with, in the broadest sense, the voting members' report.

I guess getting from individual yes, no, maybe, judgments on individual subtopics, particularly in chapter 5 where it's so complex, it will be kind of a narrative, interpretive summary that gets the analysis into the equipoise paradigm, because I guess I can't think of any other way to get some of these snippets of individual yes/no questions regarding menthol versus non-menthol into weight of evidence, other than kind of a narrative treatment.

Is that the way we --

DR. SAMET: I think that actually is the, if

you will, standard, perhaps absent any other sort of approach, whether it's in the surgeon general's report, an EPA document, or something else, really. I think taking a uniform approach -- and we will have, across these chapters, reviewed the most critical evidence, identified it, evaluated it for its strengths, and weakness, and relevance. And then, I would say that for each question, there would be, as you say, a narrative that would address the evidence, its strengths, and weaknesses.

I think we are also faced with issues of subpopulations and generalized ability of findings that we need to touch on, and that that narrative would then support what, in the end, will be a classification of the strength of evidence for a relationship in the four levels that we have proposed.

DR. HECK: I think we'll all have to be on guard, though, against subjectivity creeping into this narrative process, because even the phrasing of some of the questions we saw as they were posed,

to my mind, implies -- maybe bias is too small a word. But it introduces the possibility of subjectivity creeping into the process, and we'll all have to be on guard against that.

DR. HATSUKAMI: Jon, as I had mentioned before, we are going to have some tables constructed as well. So that will provide some of the specific results. And they'll provide information in terms of what the basis was for a particular evaluation.

DR. SAMET: I mean, I think subjectivity is perhaps the wrong word. I mean, I think the conclusions will, of course, be framed by committee judgment. I think what we are trying to make clear, and I think this goes back to the principles that were set out in chapter 1 and 2, is that we will set out the evidence on which these decisions are based. We've tried to supply a clear structure for decision making, and the evidence will be there.

Yes, at least for the voting members, the judgment will be a collective one from us,

reflecting our scientific judgments and evaluation of complex evidence. And I think, in a sense, I don't think this practice differs from the kinds of judgments made in many other contexts.

Mark, do you want to elaborate?

DR. CLANTON: No.

DR. HECK: Yes. It's just such a bewildering diversity of subtopics we have here. And there's very few for which there is not -- if not contrary at least inconsistent evidence one way or the other. Translating that into a weight of quality and evidence is going to really be Mark's challenge here, and in fact, indeed, the committee's challenge because we have some yeses, some maybes, some nos, and some equivocals throughout most of this literature. And that's the work that remains.

DR. SAMET: No. I mean, there's no doubt that you're anticipating a difficult task of judgment in the face of uncertainty. That said, the four-level classification does acknowledge the existence of uncertainty. And I think our report,

again, will be cleared to highlight where the gaps are, because I think one other output of our report -- and I think perhaps Mark didn't give too much emphasis to this in his presentation -- will be for those gaps that are most critical, I think we will make recommendations moving forward for what additional evidence might be generated to add to certainty. But I think you're correctly anticipating the challenge ahead.

Mark?

DR. CLANTON: I do want to underline your previous statement that it's not unusual in scientific deliberations, and particularly where we're blending clinical evidence with scientific evidence -- it's not unusual that judgments get made. And those judgments are often made based on an expert opinion or set of opinions.

So this sort of goes back to some comments earlier about is there going to be a randomized clinical trial showing causality on every issue we engage, and the answer is no. So we'll use the evidence.

Again, I think transparency may be the most important issue here, which is here's the evidence that we used in order to derive certain judgments and conclusions. And that process is identical to any process in IOM deliberations and other types of scientific deliberations.

DR. BACKINGER: So my question is around recommendations, because I think that the regulation specifies that you're going to write a report and make recommendation. And, Jon, you just mentioned recommendations around future research. And I guess my question is the extent to which you're going to make recommendations in a whole host of areas.

So for example, yesterday, it came up around the issue of contraband. And there was discussion that if menthol were to be banned, that you would need to have some time in order to do a public educational campaign. So I guess I'm just wondering -- and then just now, someone asked about -- I think Mark asked Neal about criteria for a ban. So I'm wondering the extent to which

recommendations will be made in this report.

DR. SAMET: I'm trying to decide whether to punt to Mark or say stay tuned. I mean, I think it'll be useful to have just some discussions. I mean, obviously, Cathy, it would be premature at this point to sort of anticipate the exact form of our findings and recommendations. I do think that we will obviously speak to our direct charge related to menthol cigarettes. We will provide answers to the questions.

Then I think that the next matter will be what kinds of recommendations we make with regard to public health, public health protection. And I think additional considerations related to some of the potential risks, example, contraband, sort of benefits, population -- a large population may decide that it's time to quit, and then, also to address any gaps in understanding or gaps in surveillance systems.

I mean, I think there'll be a number of ways that our recommendations might be said and framed, and a number of topics that they might address.

But I think, at this point, these are only matters of conjecture as to what we may do. I don't think we've had very much discussion on that. I do think the next meeting, probably, is the one where we will really have to begin to hone in.

Mark?

DR. CLANTON: I just want to add to what you just said.

So, Cathy, for example, we know for a fact there's going to be a set of recommendations related to gaps in knowledge in particular areas. So it's going to be absolutely certain that we'll list recommendations about how to get rid of those gaps to improve our knowledge base in certain critical areas.

There'll be, absolutely, recommendations about public health as it relates to menthol, because we shouldn't forget that it's about menthol, nicotine, and cigarettes, at large, even though we've been asked to look at menthol. And there are going to be some straightforward recommendations about public health.

But to Jon's point, I don't think we can begin to predict other kinds of recommendations that might come forward to the FDA until we've really gotten our arms around a first, maybe even second draft.

DR. BACKINGER: Thanks for that clarification. I think just hearing that -- I mean, it hadn't been brought up previously as everyone walked through the chapters, about recommendations. So having at least that context is helpful.

DR. CLANTON: Mr. Chairman, again, we haven't decided yet whether those recommendations will flow individually, at the end of each chapter, or whether we aggregate them in chapter 7, or maybe they're repeated. But that's sort of a logistic, editorial decision that we haven't made yet.

DR. SAMET: Dorothy?

DR. HATSUKAMI: I would think that we should do that in each of the chapters, because we certainly have the most knowledge. So then you can pull them together.

DR. SAMET: I think that would be useful to chapter authors. Identify those, and they can be at the end and then resummarized.

Other comments on chapter 7?

[No response.]

Committee Discussion

DR. SAMET: Okay. Well, while it hasn't taken shape yet, by March 23rd, it will. Okay. Why don't we look at the questions to the committee? And I think, again, these were general discussion questions that I think we might spend a few moments on.

If we have specific comments -- I mean, we made some -- we gave David Mendez some feedback yesterday. But if there are additional comments about the model, it would be useful to offer them to him as soon as possible.

Corinne?

DR. HUSTEN: Well, I think that was the question I was going to raise, is that, presumably, it will take him time to run the model or models after he gets estimates from the various writing

groups and parameters around the ranges and things.

So I'd just encourage, at least, some preliminary estimates be provided so that he can come back at the next meeting with something to present, so he can get further feedback and comments. But, presumably, that's not something he can do overnight.

DR. SAMET: I don't know that each of the groups, each of the chapter groups, has a clear enough understanding of what David might need.

Do you at this point or would you like, sort of, more clear directions from him, a list, for example, around the experiment and initiation? What would you like? Comparative rates? For example, he would probably want a comparative rate of initiation in menthol, smokers of menthol cigarettes versus non, some range around that, and so on.

So would it be helpful to get a list back, just to make sure you know what to fill in the blanks on? Dorothy?

DR. HATSUKAMI: Yes. I think that would be

very helpful, to have the specific information that David needs to put into his model. And so, yes, that would help in terms of constructing the tables as well.

DR. SAMET: Anything else on the model? Yes, Dan?

DR. HECK: I just had kind of a broad sense of the first I'd seen of the model laid out yesterday. I can see this, the diagram, let's say filled in completely in some fashion, with various steps in the model, with more or less consistent, or coherent, or inconsistent data. But we have, on the far right of the model, the ultimate outcome, occurrence of disease, relatively in menthol and non-menthol smokers.

Actually, there's never enough, but we have certainly more studies, epi studies on this ingredient or this cigarette design feature, second only to perhaps tar yield or filters, some of the earlier work. We have, one step back from that, the biomarkers of exposure that I know Neal is going to be detailing, that really, I think is fair

to say, on nearly all, if not all, of the major larger studies that show no real difference in exposure, biomarkers of exposure, which steps back to informing smoking topography, smoking style. I guess the ultimate measure of cessation is the large cessation studies. We don't, in my view, see any prominent differences in those.

So I don't want us to get too confused with all the intervening steps because we kind of know, in my view, how this continuum comes out. Now, the societal impact of the presence of menthol on initiation and the contraband questions, that's a little different element that's not as quantifiable, perhaps. But we do have, at least in some of those areas, pretty sound, quantifiable methods to measure the net effect, comparative effect. And so, I just don't want us to get too bogged down in all the intervening steps because we kind of are fairly well informed on the exposure and ultimate risks. That's just a comment.

DR. SAMET: Just to comment, I heard the presentation yesterday. It's just really a

reminder. And I think this is where the model becomes useful, that the burden of attributable, either disease or premature mortality, depends not only on the relative risks but on the number of people who are smoking.

For example, the relative risks could be the same for smokers of menthol and non-menthol cigarettes. But if the existence of menthol cigarettes doubled the number of smokers, there would be a substantial public health burden. So in terms of thinking about the public health burden, understanding the risks is important, the relative risk estimates. And that will be the focus in part of chapter 6. But the other piece – and, again, this is where the model figures in -- is to try and understand the consequences of having menthol cigarettes for, essentially, what the size of the pull of people at risk is. So that's the other important piece and where I think the model will be helpful.

DR. HECK: Yes. I guess we'll have to necessarily be speculative, if the world were

different, if the world had been different, what the outcome may or may not have been. But that's just the task we have before us.

DR. SAMET: Again, I think here we're following, I think, very standard approaches that have been applied to sort of burden estimation of public health impact assessment.

I'm sorry. I just want to make sure. I will get from David a list specifically of what he would like, and I think that this is something that I could work on with him.

Neal?

DR. BENOWITZ: One thing we asked David to do, and he may want to start work on this now, is doing some race ethnicity-specific models. I don't think he's ever published that before. And we just want to make sure that he can do that, and he has the appropriate data to do it.

DR. SAMET: Good point.

So anything else with the model?

[Dr. Clanton shakes head no.]

DR. SAMET: No? Corinne?

DR. HUSTEN: Well, one of the things that had come out yesterday is about whether the age for initiation should be pushed back to a later age, given the racial, I think, differences in initiation. And I think some data was presented, maybe in Karen's and Patricia's slides, around age of initiation by race and stuff. I can't remember. I feel like I saw something today.

DR. SAMET: Yes. So he needs to expand out that piece of the model, Corinne.

Okay, number 2. Now this, I think, really relates back to chapters 1 and 2. And so, I think the question for the committee is whether there is anything additional beyond what we discussed yesterday, recognizing that it was the end of the day and we may not have been at our best. We probably weren't at our worst.

So any additional thoughts? So there, we talked about the strategy. We talked about the principles. We talked about the evidence classification system. I think we identified some things that we needed to really amplify out, and

sort of the sources of evidence, and kind of what they are and how we're approaching the different bodies of evidence.

Yes, Neal?

DR. BENOWITZ: I think we included this, but there are some areas of research where we don't have published data. We may have industry documents or reports of summaries of research in the industry. And we just have to basically say that where we have no other information, we will look at this information with the caveat that we have not been able to look at primary data sources.

DR. SAMET: Okay. Anything else on number 2 here?

[No response.]

DR. SAMET: There must be a 3. Okay?

DR. KAROL: My job here is just to remind you that Native Americans, of course, use tobacco for traditional means, and that somewhere in this, there should be a sentence to include the fact that this isn't taking into account the tobacco use for ceremonial use.

DR. SAMET: Okay. I think we just need a reminder on that issue. Thank you.

DR. BACKINGER: Is Patricia on the phone? I guess I'm not aware that Native Americans would be using menthol cigarettes for ceremonial use. But it's just a question.

Patricia, are you there?

DR. HENDERSON: This is Patricia. We don't have that information available. There are many tribes throughout the country that use what we call commercial tobacco for ceremonial purposes. That could include menthol cigarettes, so we don't have that information, though.

DR. KAROL: I don't have any specific knowledge of specific use of mentholated tobacco for ceremonial, but we do use some commercial products.

DR. HENDERSON: Right. So it could be menthol cigarettes.

DR. KAROL: It might end up being mentholated, but I don't think it's specifically for the ceremonial event, that I'm aware of.

DR. SAMET: Okay. Thank you.

Anything else on 2?

[No response.]

DR. SAMET: Three, what suggestions does TPSAC have regarding the strength of evidence criteria? And, again, I think we've now discussed those on several occasions. I think we are able to explain why we have gone to this four-level approach, why equipoise is, in part, useful. It's, we hope, an identifiable point, and one where a level of certainty at equipoise or above may have potential value for decision makers.

So I think we'll be able to explain why we're doing what we're doing with our classification of evidence, further revisiting our comments at this point. I think we just have to make sure we're all in consensus, if you will, about this.

Yes, Jack?

DR. HENNINGFIELD: When I reflect back on our discussions today and yesterday, I think that the approach to the strength of evidence really

works because it's very clear that there will be some things that I think we'll have pretty strong evidence, a number of things where it's really up in the air, and other cases where when there is an effect that is going in one direction but not the other. So my own sense is that this approach is a very appropriate one, and should be useful for agency decision making.

DR. SAMET: Other comments? And otherwise, I'm going to assume we're comfortable with what we said we're doing.

Okay. Number 4. That's been our last five or six hours of work. I think we don't need to talk, per se, about the chapter writing groups. I think, Caryn, this is probably a good time to just reflect on schedule, and our next meetings, and what is coming up. And I think this is all in anticipation of our March 23rd deadline. So we're back together February 10-11.

Do you want to say, sort of, the structure of those two days?

MS. COHEN: On February 10th, we have a

meeting of the TPSAC. It's going to be a closed meeting in the morning from 8:00 a.m. to noon. And at 1:00, from 1:00 to 5:00 p.m., it's going to be an open session. On February 11th, we have a meeting of the Menthol Subcommittee.

Then we have future proposed meetings that have not been posted yet, but we are hoping to have a meeting March 1st and 2nd. Again, the March 1st meeting would be the full TPSAC closed meeting from 8:00 until 10:00, and then an open meeting in the afternoon, and another meeting of the subcommittee on March 2nd.

DR. SAMET: Okay. So we have opportunity to be together. I think probably most critical is looking, as these chapters develop, at where the conclusions are, and I think really having the opportunity to have some discussion among all of us about the shaping of chapter 7 and bringing together the evidence across the chapters will be important. I don't know.

Melanie, what are your plans for these various trips?

DR. WAKEFIELD: I'll be here.

DR. SAMET: You'll be here? You might as well just stay here.

Okay. Then, Corinne, yes?

DR. HUSTEN: We'll have to figure out the logistics across the meetings, but it's going to be important for each of the chapters to lay out what the evidence is and their conclusions about the chapters. And, again, we can work out -- is that in the subcommittee open meeting or is it part of the full TPSAC? And then obviously once the evidence has been discussed and debated, then a discussion of potential recommendations.

So, again, we'll work with you around the logistics of how all that gets done between now and when the report is due. But those two things, obviously, are very important that they occur in an open meeting.

DR. SAMET: I might make a comment. I think I can speak on behalf of all of TPSAC that it would be great on the second day to finish meetings in time to escape. And I think, probably, what is

most critical is that for those of us who want to head west, at least if we count on getting to Dulles by the sort of 5:00 bank of flights, by 4:00. And we understand that no matter where we are, we have to deal with the Beltway to get to Dulles, whether it's here or in the Gaithersburg, site, or somewhere else. It's probably easiest to get to Dulles from downtown because of the HOV thing on 66.

So if we could plan, we don't mind starting at 8:00 and getting going and somewhat, but I think that means, if we want to get to Dulles by 4-ish, we need to be on the road by 3:00 at the latest, I think, probably from here or from the other location. So if you guys could keep that in mind, I know Neal and I would like that, Mark probably.

DR. CLANTON: Absolutely.

DR. SAMET: So if we could just plan on the second day. And the first day, I don't think any of us mind going a little later if that's possible, in fact.

Yes, John?

DR. LAUTERBACH: These closed meetings that are being scheduled, are those for the menthol data or are those for another topic?

DR. HUSTEN: Those are to present the commercial confidential information from the industry documents on menthol. And they may not all be needed, but we have to put in the requests for these meetings months ahead. And so we wanted to have time blocked out in case the committee felt like they needed to discuss the commercial confidential information more. And if they don't, we can just go straight to open meeting.

DR. SAMET: Dorothy?

DR. HATSUKAMI: Just to ask a process question, Corinne, if we do want to have further analysis of data, do I let you know directly, or what's the process of that?

DR. HUSTEN: Yes, let Caryn know.

DR. HATSUKAMI: Okay.

DR. HUSTEN: Again, we'll do the best we can within the time constraints.

DR. SAMET: Okay. Any other matters we want

to discuss?

[No response.]

Adjournment

DR. SAMET: Okay. Then I think we're adjourned. I want to thank everyone for hard work, the public for their input, staff for keeping us organized. So we will see you in February. We're promised no snowstorm.

(Whereupon, at 11:05 a.m., the meeting was adjourned.)